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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,624	12/06/2005	Peter Bromley	2590-143	2816

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/559,624	BROMLEY, PETER	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claim 1 is objected to because of the following informalities: Claim 1 fails to have a period at the end of the sentence. Claim 1 also misspells the word transfected as "trasnfected". Appropriate correction is required.

2. Claim 2 is objected to because of the following informalities: Claim 2 is dependent on claim 1, but uses the phrase claim "one" instead of the numerical value. Appropriate correction is required.

3. Claim 3 is objected to because of the following informalities: Claim 3 is dependent on claim 1, but uses the phrase claim "one" instead of the numerical value. Appropriate correction is required.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract uses legal phraseology "said" and is missing a period at the end of the last sentence. Additionally the abstract misspells the word transfected as "trasnfected". Correction is required. See MPEP § 608.01(b).

5. The disclosure is objected to because of the following informalities: Page1, line 5 is missing punctuation at the end of the sentence.

6. Page 5, line 3 is missing punctuation at the end of the sentence.

7. Page 15, line 1 is missing a semicolon at the end of the sentence and line 2 is missing a period at the end of the sentence.

8. The preliminary amendment on 12/06/2005 to the specification at page 5, line 6 leaves a closed parenthesis symbol without a corresponding open parenthesis.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase, "normal growth temperatures" of the host cells. What are "normal growth temperatures"? The specification fails to define this term. Does this term refer to the "normal" temperature for growing untransfected cells in culture? Do different cell lines grow at slightly different "normal" growth temperatures? A skilled artisan would be unable to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsang et al (US Patent Application Publication US 2003/0207832 A1). Claims 1-2 state a method for producing competent gene products in human cells, comprising providing a DNA construct in which a gene of interest is operably linked to a modified heat-inducible promoter, introducing the DNA construct into a human cell line, and subjecting the transformed cell line to a transient increase in temperature, whereby permitting the translation of the gene of interest to occur (claim 1) and where in the method is further limited in which the modified heat inducible promoter is the Hi-Hot promoter (claim 2).

13. Tsang et al teaches a method of expressing a selected polynucleotide of interest under the control of a modified heat inducible promoter comprising a heat shock promoter and a second promoter operably linked to the polynucleotide of interest in a cell (claim 22). Specifically Tsang teaches that the vector include the Hi-Hot promoter (see Example 6 and figure 11). Tsang teaches that the method of gene transfer includes transfection (page 12, paragraph 136). Tsang teaches that the method

includes the heat-shock conditions of the transfected cell which can comprise temperature ranges of 37°C to 42°C. Tang teaches the method in which transfected cells are cultured at 37°C and subjected to 41-42°C 1 hour heat shock periods and subsequently returned to 37°C in Interleukin amplifier experiments (page, 19, paragraph 220). Tsang teaches that the recombinant vectors can be expressed in human cell lines DU-145, MCF-7 (page 17, paragraph 193). Thus Tsang teaches the claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsang et al (US Patent Application Publication US 2003/0207832 A1) as applied to claims 1-2 above, and further in view of Runge et al (Biochemical and Biophysical Research Communications, 2000). Claims 3-6 state a method for producing competent gene products in human cells, comprising providing a DNA construct in which a gene of interest is operably linked to a modified heat-inducible promoter, introducing the DNA construct into a human cell line, and subjecting the transformed cell line to a transient increase in temperature, whereby permitting the translation of the gene of interest to occur (claim 1) wherein the human cell line is a competent human hepatocytes cell line (claim 3) wherein the gene expressed encodes a therapeutic protein (claim 4) wherein

the therapeutic gene is further limited to interferons, interleukins, blood clotting factors, insulins, growth hormone, urokinase, EOP, TPA, FSH, somatostatin, etc. (claim 5) and wherein the method is further limited to express a natural liver protein as the gene of interest (claim 6).

16. Tsang et al teaches a method of expressing a selected polynucleotide of interest under the control of a modified heat inducible promoter comprising a heat shock promoter and a second promoter operably linked to the polynucleotide of interest in a cell (claim 22). Specifically Tsang teaches that the vector include the Hi-Hot promoter (see Example 6 and figure 11). Tsang teaches that the method of gene transfer includes transfection (page 12, paragraph 136). Tsang teaches that the method include the heat-shock conditions of the transfected cell comprise temperature ranges of 37°C to 42°C. Tsang teaches that the recombinant vectors can be expressed in human cell lines DU-145, MCF-7 (page 17, paragraph 193). Tsang teaches that the method can be employed in vitro (claim 39), and that the gene of interest to be expressed is a therapeutic gene (claim 43). Tsang teaches that the vector can be expressed in a multitude of cells including brain, liver, bladder, spleen, kidney, lymph node, blood cells, muscle cells etc. (claim 38). Tsang teaches that the vector can encode for interleukins and the natural liver proteins Interferon-α (INF-α) and Intercellular adhesion molecule 1 (I-CAM 1) (claim 35). Tsang does not specifically teach that the human cell line used to express the vector is a competent human hepatocytes cell line.

17. Runge et al (Biochemical and Biophysical Research Communications, 2000) teaches that long-term human hepatocytes cultures are important tools for

pharmacological and toxicological liver studies (page 1, column 2, lines 35-37). Runge specifically states that human hepatocytes are necessary to study liver-specific processes and functions because "interspecies differences in all aspects of hepatocytes function exist" and differences include intracellular distribution of gluconeogenic enzymes, apolipoprotein A-IV expression, metabolic regulation of cholesterol and triacylglycerol synthesis as well as cytochrome P450 induction have been reported (page 1, first paragraph). Additionally, Runge reports investigators using immortalized human hepatocyte cell lines for gene therapy purposes for the treatment of familial hypercholesterolemia (page 2, first full paragraph).

18. The skilled artisan would have been motivated to combine the teachings of Tsang on the method of producing therapeutic gene products (including interleukins, and native liver proteins) in a human cell line utilizing a DNA vector driven by a modified heat-inducible promoter with the teaching of Runge et al on the usefulness of human hepatocytes cell culture lines for the investigation of liver functions to overcome interspecies differences in culture hepatocytes because the modified heat inducible system allows for, "the ability to express therapeutic gene(s) at very high levels and the ability to control the levels of expression" (page 4, paragraph 50) and using this system in human hepatocyte cell culture ensures that proper native protein production occurs (ie specific human proteins) in order to treat specific human liver derived diseases (such as hypercholesterolemia). It would have been obvious to the skilled artisan to combine the teaching of Tsang on the method of producing therapeutic gene products (including interleukins; and native liver proteins) in a human cell line utilizing a DNA vector driven

by a modified heat-inducible promoter with the teaching of Runge et al on the usefulness of human hepatocytes cell culture lines for the investigation of liver functions to overcome interspecies differences in cultured hepatocytes because the versatility of the heat-inducible system designed by Tsang is able to be used in a multitude of cell types, including liver cells, and that human hepatocyte cell lines over-come many deficiencies of using non-human cell lines and would allow for more accurate treatment of and investigation into human liver-specific diseases. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KAM/07/17/06

DAVID GUZO
PRIMARY EXAMINER